

# NIOSH Skin Notation Profiles

## Aniline

SK

ID<sup>SK</sup>

[SK]

SYS

SYS (FATAL)

DIR

DIR (IRR)

DIR (COR)

SEN

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# NIOSH Skin Notation (SK) Profile

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**Aniline**

**[CAS No. 62-53-3]**

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**Naomi L. Hudson and G. Scott Dotson**

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## Foreword

As the largest organ of the body, the skin performs multiple critical functions, such as serving as the primary barrier to the external environment. For this reason, the skin is often exposed to potentially hazardous agents, including chemicals, which may contribute to the onset of a spectrum of adverse health effects ranging from localized damage (e.g., irritant contact dermatitis and corrosion) to induction of immune-mediated responses (e.g., allergic contact dermatitis and pulmonary responses), or systemic toxicity (e.g., neurotoxicity and hepatotoxicity). Understanding the hazards related to skin contact with chemicals is a critical component of modern occupational safety and health programs.

In 2009, the National Institute for Occupational Safety and Health (NIOSH) published *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009-147]. This document provides the scientific rationale and framework for the assignment of multiple hazard-specific skin notations (SK) that clearly distinguish between the systemic effects, direct (localized) effects, and immune-mediated responses caused by skin contact with chemicals. The key step within assignment of the hazard-specific SK is the determination of the hazard potential of the substance, or its potential for causing adverse health effects as a result of skin exposure. This determination entails a health hazard identification process that involves use of the following:

- Scientific data on the physicochemical properties of a chemical
- Data on human exposures and health effects
- Empirical data from *in vivo* and *in vitro* laboratory testing
- Computational techniques, including predictive algorithms and mathematical models that describe a selected process (e.g., skin permeation) by means of analytical or numerical methods.

This *Skin Notation Profile* provides the SK assignments and supportive data for aniline. In particular, this document evaluates and summarizes the literature describing the hazard potential of the substance and its assessment according to the scientific rationale and framework outlined in CIB 61. In meeting this objective, this *Skin Notation Profile* intends to inform the audience—mostly occupational health practitioners, researchers, policy- and decision-makers, employers, and workers in potentially hazardous workplaces—so that improved risk-management practices may be developed to better protect workers from the risks of skin contact with the chemicals of interest.

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## Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ATSDR	Agency for Toxic Substances and Disease Registry
CIB	Current Intelligence Bulletin
cm <sup>2</sup>	square centimeter(s)
cm/hr	centimeter(s) per hour
cm/s	centimeter(s) per second
<i>DEREK</i>	Deductive Estimation of Risk from Existing Knowledge
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
EC	European Commission
g	gram(s)
g/L	gram(s)/liter
GHS	Globally Harmonized System for Classification and Labelling of Chemicals
GPMT	guinea pig maximization test
hr	hour(s)
IARC	International Agency for Research on Cancer
IPCS	International Program for Chemical Safety
(IRR)	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
$k_{aq}$	coefficient in the watery epidermal layer
$k_p$	skin permeation coefficient
$k_{pol}$	coefficient in the protein fraction of the stratum corneum
$k_{psc}$	permeation coefficient in the lipid fraction of the stratum corneum
LD <sub>50</sub>	dose resulting in 50% mortality in the exposed population
LD <sub>Lo</sub>	dermal lethal dose
LLNA	local lymph node assay
LOAEL	lowest-observed-adverse-effect level
log $K_{OW}$	base-10 logarithm of a substance's octanol–water partition
$M$	molarity
m <sup>3</sup>	cubic meter(s)
mg	milligram(s)
mg/cm <sup>2</sup> /hr	milligram(s) per square centimeter per hour
mg/kg	milligram(s) per kilogram body weight
mg/m <sup>3</sup>	milligram(s) per cubic meter
mL	milliliter(s)
mL/kg	milliliter(s) per kilogram body weight
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level

NTP	National Toxicology Program
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
ppm	parts per million
REL	recommended exposure limit
RF	retention factor
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SI ratio	ratio of skin dose to inhalation dose
SK	skin notation
$S_w$	solubility in water
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
US EPA	United States Environmental Protection Agency
$\mu\text{g}$	microgram(s)
$\mu\text{g}/\text{cm}^2$	microgram(s) per square centimeter
$\mu\text{g}/\text{cm}^2/\text{hr}$	microgram(s) per square centimeter per hour
$\mu\text{L}$	microliter(s)
$\mu\text{mol}$	micromole(s)

## Glossary

**Absorption**—The transport of a chemical from the outer surface of the skin into both the skin and systemic circulation (including penetration, permeation, and resorption).

**Acute exposure**—Contact with a chemical that occurs once or for only a short period of time.

**Cancer**—Any one of a group of diseases that occurs when cells in the body become abnormal and grow or multiply out of control.

**Contaminant**—A chemical that is (1) unintentionally present within a neat substance or mixture at a concentration less than 1.0% or (2) recognized as a potential carcinogen and present within a neat substance or mixture at a concentration less than 0.1%.

**Cutaneous (or percutaneous)**—Referring to the skin (or through the skin).

**Dermal**—Referring to the skin.

**Dermal contact**—Contact with (touching) the skin.

**Direct effects**—Localized, non-immune-mediated adverse health effects on the skin, including corrosion, primary irritation, changes in skin pigmentation, and reduction/disruption of the skin barrier integrity, occurring at or near the point of contact with chemicals.

**Immune-mediated responses**—Responses mediated by the immune system, including allergic responses.

**Sensitization**—A specific immune-mediated response that develops following exposure to a chemical, which, upon re-exposure, can lead to allergic contact dermatitis (ACD) or other immune-mediated diseases such as asthma, depending on the site and route of re-exposure.

**Substance**—A chemical.

**Systemic effects**—Systemic toxicity associated with skin absorption of chemicals after exposure of the skin.

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# 1 Introduction

## 1.1 General Substance Information

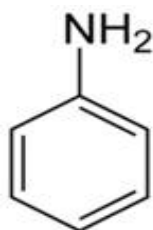
**Chemical:** Aniline

**CAS No:** 62-53-3

**Molecular weight (MW):** 93.1

**Molecular formula:** C<sub>6</sub>H<sub>5</sub>NH<sub>2</sub>

**Structural formula:**



**Synonyms:**

Aminobenzene, Aniline oil, Benzenamine, Phenylamine

**Uses:**

Aniline is primarily used in the manufacturing of dyestuffs, as a chemical intermediate, and as a rubber accelerator [Weisburger and Hudson 2001]. In addition, an estimated 900 million pounds (~409 million kilograms) of aniline were produced in 1992 [Weisburger and Hudson 2001].

## 1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with aniline and (2) the rationale behind the hazard-specific skin notation (SK) assignment for aniline. The SK assignment is based on the scientific rationale and logic outlined in the *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009]. The summarized information and health hazard assessment are limited to an evaluation of the potential health effects of dermal exposure to aniline. A literature search was conducted through August 2014 to identify information on aniline, including but not limited to data relating to its toxicokinetics,

acute toxicity, repeated-dose systemic toxicity, carcinogenicity, biological system/function-specific effects (including reproductive and developmental effects and immunotoxicity), irritation, and sensitization. Information was considered from studies of humans, animals, or appropriate modeling systems that are relevant to assessing the effects of dermal exposure to aniline.

## 1.3 Overview of SK Assignment

Aniline is potentially capable of causing numerous adverse health effects following skin contact. A critical review of available data has resulted in the following SK assignment for aniline: **SK: SYS-SEN**. Table 1 provides an

**Table 1. Summary of the SK assignment for aniline**

Skin notation	Critical effect	Available data
SK: SYS	Methemoglobinemia	Limited human and sufficient animal data
SK: SEN	Skin allergy	Limited human and sufficient animal data

overview of the critical effects and data used to develop the SK assignment for aniline.

## 2 Systemic Toxicity from Skin Exposure (SK: SYS)

Toxicokinetic studies following dermal exposure to aniline in humans and animals were identified. Dutkiewicz [1961] conducted 20 experiments to determine the potential of dermal absorption in humans exposed to aniline vapor for up to 5 hours. Dutkiewicz [1961] reported an average dermal absorption of 25.6–33 micrograms per square centimeter per hour ( $\mu\text{g}/\text{cm}^2/\text{hr}$ ) and  $15.0 \mu\text{g}/\text{cm}^2/\text{hr}$  with use of work clothing (i.e. overalls). In an industrial setting, Dutkiewicz [1961] reported that 26.5% and 50% of the dose of aniline were dermally absorbed from vapor and liquid exposures, respectively. Other factors reported to affect percutaneous absorption of aniline included temperature, moisture, humidity, exposure duration and concentration of aniline applied [Piotrowski 1957; Dutkiewicz 1961]. Baranowska-Dutkiewicz [1982] found that absorption rates of aniline increased with evaluated concentrations and decreased with longer exposure times when 10 volunteers were exposed to solutions of 1–2% aniline for 30 or 60 minutes. Baranowska-Dutkiewicz [1982] also reported dermal absorption rates of 3.0 milligrams per square centimeter per hour ( $\text{mg}/\text{cm}^2/\text{hr}$ ) and  $2.5 \text{ mg}/\text{cm}^2/\text{hr}$  from liquid aniline and aniline with 3% water, and  $0.20\text{--}1.22 \text{ mg}/\text{cm}^2/\text{hr}$  from aqueous solution (1–2% in water), following 30 or 60 minute dermal applications of dilute aqueous solutions of aniline to human skin *in vivo*. Piotrowski [1957] reported dermal absorption rates of 0.18 to  $0.72 \text{ mg}/\text{cm}^2/\text{hr}$  in 15 tests conducted on 11 human subjects exposed to aniline on the forearm under gauze for 5 hours and  $3.8 \text{ mg}/\text{cm}^2/\text{hr}$  when the gauze was moistened with water and the subjects exposed for 1 hour. In mice, Susten et al. [1990] calculated a dermal absorption of 4.7% of the applied dose and an absorption rate of  $2.3 \text{ mg}/\text{cm}^2/\text{min}$ .

*In vitro* studies using human and animal skin were also identified. Barry et al. [1985] reported that permeation of aniline *in vitro* through dermatomed human abdominal cadaver skin was  $1870 \mu\text{g}/\text{cm}^2/\text{hr}$  for pure liquid,  $760 \mu\text{g}/\text{cm}^2/\text{hr}$  for saturated aqueous solution,  $260 \mu\text{g}/\text{cm}^2/\text{hr}$  for the vapor of the pure liquid, and  $250 \mu\text{g}/\text{cm}^2/\text{hr}$  for vapor of saturated aqueous solution. Korinth et al. [2012] reported the flux of aniline was  $725.2 \mu\text{g}/\text{cm}^2/\text{hr}$  using Franz diffusion cells in close agreement with OECD guideline 428. The potential of aniline to pose a skin absorption hazard was also evaluated, with use of a predictive algorithm for estimating and evaluating the health hazards of dermal exposure to substances [NIOSH 2009]. The evaluation method compares an estimated dose accumulated in the body from skin absorption and an estimated dose from respiratory absorption associated with a reference occupational exposure limit. On the basis of this algorithm, a ratio of the skin dose to the inhalation dose (SI ratio) of 2.28 was calculated for aniline. An SI ratio of  $\geq 0.1$  indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, aniline is considered to be absorbed through the skin following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No dermal lethal doses ( $\text{LD}_{50}$ 's) of aniline in humans have been identified. The dermal  $\text{LD}_{50}$  value (the dose resulting in 50% mortality in the exposed animals) was  $0.82 \text{ mL}/\text{kg}$  [corresponding to  $838 \text{ mg}/\text{kg}$ , based on density of  $1.0217 \text{ g}/\text{mL}$ ] when applied to abraded rabbit skin and  $2.15 \text{ mL}/\text{kg}$  [corresponding to  $2200 \text{ mg}/\text{kg}$ ] and  $1.29 \text{ mL}/\text{kg}$  [corresponding to  $1318 \text{ mg}/\text{kg}$ ] when applied to abraded and intact guinea pig skin, respectively [Roudabush et al. 1965]. Dow Chemical Company [1940] found dermal application of  $2400 \text{ mg}/\text{kg}$  to produce no lethality when administered to rabbits, while doses greater than  $3000 \text{ mg}/\text{kg}$  produced 100% mortality. Because the reported acute dermal  $\text{LD}_{50}$  values for guinea pigs and rabbits are generally lower than the critical dermal  $\text{LD}_{50}$  value of  $2000 \text{ mg}/\text{kg}$

kg body weight that identifies chemical substances with the potential for acute dermal toxicity [NIOSH 2009], aniline demonstrates acute toxicity following dermal exposure.

Numerous instances of accidental and occupational exposures to aniline have been reported. Two cases of accidental spraying of the skin with aniline reported symptoms including discoloring of the skin, weakness, headache, sinus tachycardia, and methemoglobin (MetHb) levels of up to 70% [Phillips et al. 1990; Cummings et al. 1994]. Liao et al. [2002] reported dermal exposure to aniline in a worker. The worker was treated with methylene blue; however, methemoglobin recurred, followed by severe Heinz body hemolytic anemia. As is typical of accidental or occupational exposures, the doses of aniline that elicited these effects have not been quantified. Lee et al. [2013] reported a worker dermally exposed to 200 cc of aniline that splattered on his face and upper body. The worker suffered from a burn around the exposed skin, and showed signs of cyanoderma on his entire body. The workers' MetHb level was 46.8%, and he was diagnosed with methemoglobinemia [Lee et al. 2013]. The National Research Council

[NRC 2000] reported aniline is absorbed through the skin and is a methemoglobin-forming compound as seen in these case reports.

No repeat-dose, sub-chronic, or chronic studies of dermal exposure to aniline in humans or animals were identified. No standard toxicity or specialty studies evaluating biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to aniline were identified in animals. No assessment of the carcinogenicity of aniline following dermal exposure has been identified. However, various organizations have evaluated the potential of aniline to be carcinogenic via other routes. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for aniline.

Taken together, data from *in vivo* and *in vitro* toxicokinetic studies in humans [Piotrowski 1957; Dutkiweicz 1961; Baranowska-Dutkeiwicz 1982; Barry et al. 1985; Korin et al. 2012] indicate that aniline is dermally absorbed. The acute dermal toxicity studies

**Table 2. Summary of the carcinogenic designations\* for aniline by numerous governmental and nongovernmental organizations**

Organization	Carcinogenic designation
NIOSH [2005]	Potential occupational carcinogen
NTP [2014]	No designation
USEPA [2014]	Group B2: probable human carcinogen
European Parliament [2008]	GHS Carcinogenicity Category 2: Suspected of causing cancer
IARC [2012]	Group 3: not classifiable as to carcinogenicity to humans
EC [2014] <sup>†</sup>	R40: limited evidence of a carcinogenic effect
ACGIH [2001]	Group A3: confirmed animal carcinogen with unknown relevance to humans

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; GHS = Globally Harmonized System for Classification and Labelling of Chemicals; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; USEPA = United States Environmental Protection Agency.

\*The listed cancer designations were based on data from nondermal (such as oral or inhalation) exposure rather than dermal exposure.

<sup>†</sup>Date accessed.

in rabbits and guinea pigs [**Roudabush et al 1965**]\*, and human case reports [**Phillips et al 1990; Cummings et al. 1994; Liao et al 2002; Lee et al. 2013**] demonstrate that aniline is absorbed through the skin, and is systemically available and can cause methemoglobinemia. Therefore, on the basis of the data for this assessment, aniline is assigned the SK: SYS notation.

### 3 Direct Effects on Skin (SK:DIR)

No human or animal *in vivo* studies for corrosivity of aniline or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests of skin integrity using cadaver skin were identified. No data were identified for humans upon which the skin irritation potential of aniline can be evaluated. In rabbits, Dow Chemical Company [1940] reported aniline produced slight skin irritation.

Data that evaluated potential of aniline to cause skin irritation in animals [Dow Chemical Company 1940] are insufficient to support an IRR notation for aniline. Therefore, on the basis of the data for this assessment, aniline is not assigned the SK: DIR (IRR) notation.

### 4 Immune-mediated Responses (SK: SEN)

A number of studies were identified that evaluated the potential of aniline to cause skin sensitization in humans and animals. A recent analysis of patch test results from a contact allergy surveillance network by Uter et al. [2007] observed positive allergic reactions to aniline in 25 of 119 patients. Twenty four of the 25 patients were also positive to *para*-phenylenediamine, *p*-aminoazobenzene and (in one case) another *para*-amino compound; however, the investigators' analysis of the individual clinical data could not reveal if

the patients were exposed to aniline. Therefore, the investigators concluded that aniline was unlikely to be an independent sensitizer, but more likely to produce allergic reactions in individuals pre-sensitized to *para*-substituted amino compounds. In a human maximization test (HMT), Basketter et al. [1994] recorded positive responses in 28% of the subjects (unspecified number) induced with 20% aniline and later challenged with 10% aniline. In a database of inter-laboratory study results compiled by Haneke et al. [2001], aniline reportedly produced positive reactions in the HMT.

In animals, tests of sensitizing potential have produced equivocal results. Goodwin et al. [1981] evaluated the skin sensitization potential of aniline using three guinea pig sensitization procedures and observed positive allergic reactions in 1 of 10 animals (10%) in the guinea pig maximization test (GPMT), 5 of 10 animals (50%) in the single injection adjuvant test (SIAT), but none in the modified Draize test. Subsequently, Godwin et al. [1981] classified the potential of aniline to cause sensitization in the guinea pigs as weak in the GMPT and moderate in the SIAT, and a mild sensitizer based on their assessment of clinical data in humans. Basketter and Scholes [1992] classified aniline as an extreme sensitizer based on the 90% positive reactions in the GPMT, although the LLNA test was borderline. In a later study, Basketter et al. [2003] concluded that aniline was a weak sensitizer in the LLNA procedure. The Haneke et al. [2001] database reported aniline as a skin sensitizer in the guinea pig maximization test/Buehler assay; however, reviewing the results of the murine local lymph node assays (LLNA), negative responses were reported. The structure activity relationship model, *DEREK* for Windows, also predicted aniline to be positive regarding skin sensitization potential.

The results from the HMT [**Basketter et al. 1994; Haneke et al. 2001**], GPMTs [**Goodwin et al. 1981; Basketter and Scholes 1992**], and the weight of evidence from the murine LLNAs

\*References in bold text indicate studies that serve as the basis of the SK assignments.

[Basketter and Scholes 1992; Basketter et al. 2003], supported by the structure-activity relationship model prediction, demonstrate that aniline is a skin sensitizer. Therefore, on the basis of the data for this assessment, aniline is assigned the SK: SEN notation.

## 5 Summary

Although there is a paucity of data evaluating the systemic effects of chronic dermal exposure to aniline in humans and animals, *in vivo* and *in vitro* toxicokinetic studies in humans [Piotrowski 1957; Dutkiwicz 1961; Baranowska-Dutkeiwicz 1982; Barry et al. 1985; Korinith et al. 2012] indicate that aniline is dermally absorbed. The acute dermal toxicity studies in rabbits and guinea pigs [Roudabush et al 1965; Industrial Bio-Test Laboratories 1969], and human case reports [Phillips et al 1990; Cummings et al. 1994; Liao et al 2002; Lee et al. 2013] are sufficient to conclude that aniline is absorbed through the skin, is systemically available, and can produce methemoglobinemia. Data that evaluated potential of aniline to cause skin irritation in animals [Dow Chemical Company 1940] are insufficient to suggest that aniline produces mild skin irritation. There is sufficient data from human maximization tests [Basketter et al. 1994] guinea pig maximization tests

[Goodwin et al. 1981; Basketter and Scholes 1992], murine LLNAs (based on the weight of evidence) from [Basketter and Scholes 1992; Basketter et al. 2003] to demonstrate that aniline is a skin sensitizer. Therefore, on the basis of these assessments, aniline is assigned a composite skin notation of **SK: SYS-SEN**.

Table 3 summarizes the skin hazard designations for aniline previously issued by NIOSH and other organizations. The equivalent dermal designations for aniline, according to the Global Harmonization System (GHS) of Classification and Labelling of Chemicals, are Acute Toxicity Category 3 (Hazard statement: Toxic in contact with the skin), and Skin Sensitization Category 1 (Hazard statement: May cause an allergic skin reaction) [European Parliament 2008]. In addition, aniline has been classified as a Mutagenicity Category 2 (Hazard Statement: Suspected of causing genetic defects) [European Parliament 2008].

## References

**Note:** Asterisks (\*) denote sources cited in text; daggers (†) denote additional resources.

\*ACGIH [2001]. Aniline. In: Documentation of threshold limit values and biological exposure indices 7th ed., Vol. 1. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

**Table 3. Summary of previous skin hazard designations for aniline**

Organization	Skin hazard designation
NIOSH [2005]	No designation
OSHA [2015]*	[skin]: potential for dermal absorption
ACGIH [2001]	[skin]: based on the increase in methemoglobin in blood in animals and skin absorption in humans
EC [2014]*	R24: toxic in contact with skin R43: may cause sensitization by skin contact

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.

\*Date accessed.

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## Appendix: Calculation of the SI Ratio

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for aniline. Although the SI ratio is considered in the determination of a substance's hazard potential following skin contact, it is intended only to serve as supportive data during the assignment of the NIOSH SK. An in-depth discussion on the rationale and calculation of the SI ratio can be found in Appendix B of the *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009].

### Overview

The SI ratio is a predictive algorithm for estimating and evaluating the health hazards of skin exposure to substances. The algorithm is designed to evaluate the potential for a substance to penetrate the skin and induce systemic toxicity [NIOSH 2009]. The goals for incorporating this algorithm into the proposed strategy for assigning SYS notation are as follows:

1. Provide an alternative method to evaluate substances for which no clinical reports or animal toxicity studies exist or for which empirical data are insufficient to determine systemic effects.
2. Use the algorithm evaluation results to determine whether a substance poses a skin absorption hazard and should be labeled with the SYS notation.

The algorithm evaluation includes three steps:

1. Determining a skin permeation coefficient ( $k_p$ ) for the substance of interest.
2. Estimating substance uptake by the skin and respiratory absorption routes.
3. Evaluating whether the substance poses a skin exposure hazard.

The algorithm is flexible in the data requirement and can operate entirely on the basis of the physicochemical properties of a substance

and the relevant exposure parameters. Thus, the algorithm is independent of the need for biologic data. Alternatively, it can function with both the physicochemical properties and the experimentally determined permeation coefficient when such data are available and appropriate for use.

The first step in the evaluation is to determine the  $k_p$  for the substance to describe the transdermal penetration rate of the substance [NIOSH 2009]. The  $k_p$ , which represents the overall diffusion of the substance through the stratum corneum and into the blood capillaries of the dermis, is estimated from the compound's molecular weight ( $MW$ ) and base-10 logarithm of its octanol–water partition coefficient ( $\log K_{ow}$ ). In this example,  $k_p$  is determined for a substance with use of Equation 1. A self-consistent set of units must be used, such as centimeters per hour (cm/hr), outlined in Table A1. Other model-based estimates of  $k_p$  may also be used [NIOSH 2009].

### Equation 1: Calculation of Skin Permeation Coefficient ( $k_p$ )

$$k_p = \frac{1}{\frac{1}{k_{psc} + k_{pol}} + \frac{1}{k_q}}$$

where  $k_{psc}$  is the permeation coefficient in the lipid fraction of the stratum corneum,  $k_{pol}$  is the coefficient in the protein fraction of the stratum corneum, and  $k_{aq}$  is the coefficient in the watery epidermal layer. These components are individually estimated by

$$\log K_{psc} = -1.326 + 0.6097 \times \log K_{ow} - 0.1786 \times MW^{0.5}$$

$$K_{pol} = 0.0001519 \times MW^{0.5}$$

$$K_{aq} = 2.5 \times MW^{0.5}$$

The second step is to calculate the biologic mass uptake of the substance from skin absorption (skin dose) and inhalation (inhalation

dose) during the same period of exposure. The skin dose is calculated as a mathematical product of the  $k_p$ , the water solubility ( $S_w$ ) of the substance, the exposed skin surface area, and the duration of exposure. Its units are milligrams (mg). Assume that the skin exposure continues for 8 hours to unprotected skin on the palms of both hands (a surface area of 360 square centimeters [ $\text{cm}^2$ ]).

### Equation 2: Determination of Skin Dose

$$\begin{aligned}\text{Skin dose} &= k_p \times S_w \times \text{Exposed skin surface} \\ &\quad \text{area} \times \text{Exposure time} \\ &= k_p (\text{cm}/\text{hour}) \times S_w (\text{mg}/\text{cm}^3) \times \\ &\quad 360 \text{ cm}^2 \times 8 \text{ hours}\end{aligned}$$

The inhalation dose (in mg) is derived on the basis of the occupational exposure limit (OEL) of the substance—if the OEL is developed to prevent the occurrence of systemic effects rather than sensory/irritant effects or direct effects on the respiratory tract. Assume a continuous exposure of 8 hours, an inhalation volume of 10 cubic meters ( $\text{m}^3$ ) inhaled air in 8 hours, and a factor of 75% for retention of the airborne substance in the lungs during respiration (retention factor, or RF).

### Equation 3: Determination of Inhalation Dose

$$\begin{aligned}\text{Inhalation dose} &= \text{OEL} \times \text{Inhalation} \\ &\quad \text{volume} \times \text{RF} \\ &= \text{OEL} (\text{mg}/\text{m}^3) \times 10 \text{ m}^3 \times 0.75\end{aligned}$$

The final step is to compare the calculated skin and inhalation doses and to present the

result as a ratio of skin dose to inhalation dose (the SI ratio). This ratio quantitatively indicates (1) the significance of dermal absorption as a route of occupational exposure to the substance and (2) the contribution of dermal uptake to systemic toxicity. If a substance has an SI ratio greater than or equal to 0.1, it is considered a skin absorption hazard.

## Calculation

Table A1 summarizes the data applied in the previously described equations to determine the SI ratio for aniline. The calculated SI ratio was 2.28. On the basis of these results, aniline is not predicted to represent a skin absorption hazard.

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**Table A1. Summary of data used to calculate the SI ratio for aniline**

Variables used in calculation	Units	Value
<b>Skin permeation coefficient</b>		
Permeation coefficient of stratum corneum lipid path ( $k_{psc}$ )	cm/hr	0.00316
Permeation coefficient of the protein fraction of the stratum corneum ( $k_{pol}$ )	cm/hr	$1.5743 \times 10^{-5}$
Permeation coefficient of the watery epidermal layer ( $k_{aq}$ )	cm/hr	0.2591
Molecular weight ( $MW$ ) <sup>*</sup>	amu	93.1
Base-10 logarithm of its octanol–water partition coefficient ( $\text{Log } K_{ow}$ ) <sup>*</sup>	None	0.9
Calculated skin permeation coefficient ( $k_p$ )	cm/hr	0.00314
<b>Skin dose</b>		
Water solubility ( $S_w$ ) <sup>*</sup>	mg/cm <sup>3</sup>	36
Calculated skin permeation coefficient ( $k_p$ )	cm/hr	0.00314
Estimated skin surface area (palms of hand)	cm <sup>2</sup>	360
Exposure time	hr	8
Calculated skin dose	mg	325.1
<b>Inhalation Dose</b>		
Occupational exposure limit (OEL) <sup>†</sup>	mg/m <sup>3</sup>	19
Inhalation volume	m <sup>3</sup>	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	142.5
<b>Skin dose–to–inhalation dose (SI) ratio</b>	None	2.28

<sup>\*</sup>Variables identified from SRC [ND].

<sup>†</sup>The OEL used in calculation of the SI ratio for aniline was the NIOSH recommended exposure limit (REL) [NIOSH 2005].

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